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# Inducibility of Atrial Fibrillation Depends Chaotically on Ionic Model Parameters

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## Abstract

*Previous work has shown that fibrillation can be induced by rapid pacing in a model of the human atria without fibrosis or repolarization heterogeneity. The purpose of this study was to investigate how sensitive this type of arrhythmia induction is to model parameters.*

*Simulations were performed with a monodomain reaction-diffusion model with Courtemanche dynamics on a volumetric atrial mesh with all the major bundle structures and layered fiber orientation. The ionic model parameters were modified to represent electrically remodeled atria, uniformly. The model was stimulated with decreasing cycle length to drive the atria to maximum rate, and simulated over 10 seconds. This was tried with 10 different pacing locations and 46 different values of the conductivity,  $g_{CaL}$ , of the L-type calcium current.*

*For  $g_{CaL}$  values up to 130 % of the initial value, on average 4 out of 10 pacing sites induced AF. However, the positive sites were different for each tested  $g_{CaL}$  level, even at 1 % increments. Beyond 130 %, the AF induction rate decreased. Every pacing site yielded AF for a subset of parameter values, but some sites more frequently.*

*In conclusion, AF induction is highly sensitive to parameter values. The global decrease in induction seen for large  $g_{CaL}$  may be due to the increased wavelength.*

## 1. Introduction

Atrial fibrillation (AF) is related to both structural and electrophysiological changes in the atrial myocardium. Fibrillation promotes fibrosis, thus reducing intercellular coupling, and causes a remodeling of ionic currents that leads to shorter action potentials [1]. The resulting longer activation pathways and shorter wavelength in turn facilitate fibrillation. While this vicious circle has been well established [2], it is not clear why AF develops in some subjects and not in others. Knowledge of the initial factors could help prevention and early diagnosis.

One of the questions that computer models can help to answer is whether AF induction by rapid stimulation – from an ectopic focus or during a clinical test – is possible in non-remodeled atria. Previous work has shown that AF can be induced by rapid pacing in a model with only electrical remodeling, and that a small change in the amount of electrical remodeling can determine whether or not pacing from a given site induces AF [3]. The purpose of this study is to further characterize this dependency on parameters.

## 2. Methods

A realistic model of the atrial anatomy was previously created [3, 4] by combining imaging data with descriptions from anatomical literature [5–8]. The model consists of a thin wall (1 mm in the right atrium and 3 mm in the left) combined with endocardial muscle bundles such as the crista terminalis, pectinate muscles, and trabeculae in the left atrial appendage. It has a multi-layered fiber structure in the left atrium (LA), posterior inter-atrial bundles, and a few fiber tracts connecting the left atrium with the coronary sinus musculature (figure 1). For the simulations the model was converted into a hexahedral mesh at 0.2 mm resolution.

Electrical activity was simulated with a monodomain reaction-diffusion equation using the Courtemanche–Ramirez–Nattel model [9]. The model was slightly adapted to remove discontinuities in rate coefficients that are present in the original formulation for  $\alpha_h$ ,  $\beta_h$ ,  $\alpha_j$  and  $\beta_j$  at a transmembrane potential value of  $-40$  mV. For each of these conductivities, the coefficient was linearly interpolated between the expressions for the two sides in the interval from  $-39$  to  $-40$  mV. Similarly, linear interpolations over a 0.1-mV interval were used instead of discrete switches at each of the five singularities that are present in the model equations. The values at the singularities themselves were evaluated analytically using l'Hôpital's rule.

The parameters of the ionic model were the same for all model nodes, and were set to mimic the electrical remodeling that accompanies persistent AF:  $g_{CaL} = 0.037$ ,  $g_{TO} =$

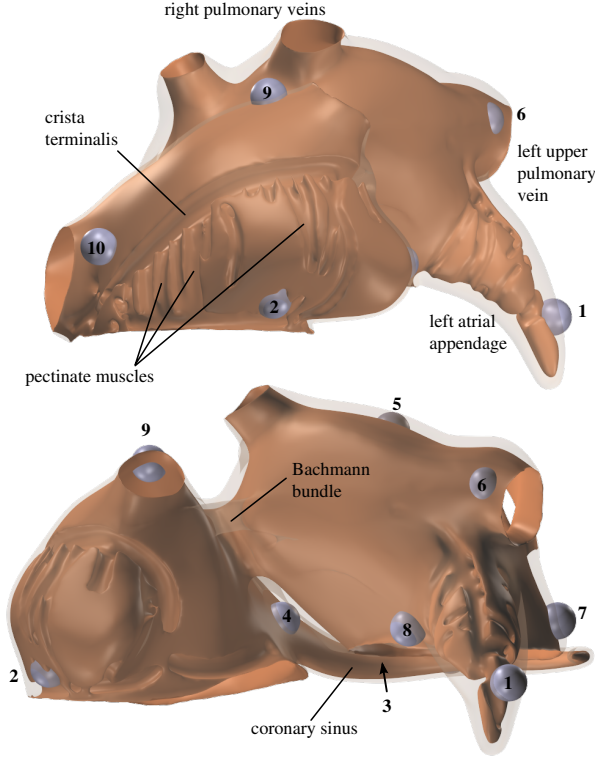


Figure 1. Renderings of the anatomical model showing the thickness variations in the atrial wall. The myocardium is semitransparent; the brown surface represents the endocardium. The blue spheres indicate the 10 pacing sites that were used.

0.026,  $g_{K1} = 0.180$ ,  $g_{Ks} = 0.1$ , and  $g_{Na} = 8.0$  nS/pF [10]. To study the effect of small parameter changes on the inducibility of AF, the value of  $g_{CaL}$  was then changed in steps of 0.1, 1, and 10 %, to cover different ranges without performing an infeasible number of simulations.

Induction of AF was attempted by delivering 14 stimuli at the same location with an interval decreasing from 280 to 124 ms. The last stimulation pulse was delivered 2088 ms after the start of the simulation. The simulation was continued until 500 ms after activation ceased, with a maximum of 10 seconds. This procedure was performed at 10 different pacing sites spread through both atria (figure 1) for 46 different levels of  $g_{CaL}$ .

The simulations were performed with a recent version of the Propag-5 code [11] either on 2048 cores of a Bullx cluster machine or on 4096 cores of an IBM BlueGene/Q. Twenty simulations were performed on both machines to verify that the results were the same despite the possible sensitivity of the model to different hardware and a different domain decomposition.

### 3. Results

The results of all 460 simulations are shown in figure 2. The figure shows the total time the model spent in self-sustained activity, which could range from 150 ms after the last pacing pulse up to the end of the simulation. Initiation of self-sustained activity was possible at each of the 10 pacing sites for one or more values of  $g_{CaL}$ , but for some sites it succeeded much more often than for others. Panel A suggests that initiation could occur over uninterrupted ranges of various widths, ranging from 1 (sites 3 and 6) to 40 percent points (site 9). Panel B, which zooms in on the range of 99 to 102 %  $g_{CaL}$ , shows that such ranges could be as short as 0.5 %, or even 0.1 % for a change from a short run to a possibly never-ending run of self-sustained activity.

The induced activity could in some cases be characterized as fibrillatory, sustained by a variable number of functional and anatomical reentries, and in other cases as atrial flutter, with a stable activation pattern controlled by anatomical reentry. The coronary sinus was often involved in such pathways.

The 20 simulations that were run on both machines, for all 10 pacing sites with 2 different values of  $g_{CaL}$ , did not show any difference between the two machines in terms of time spent in self-sustained activity.

### 4. Discussion

This study shows that rapid pacing in a model of the human atria with electrical remodeling that is typical for AF patients can induce self-sustained activity and that the success of induction is sensitive to changes in  $g_{CaL}$  as small as 0.1 % of its baseline value. In the range of 100 to 110 %  $g_{CaL}$ , the model was still active after 10 seconds in 41 out of 110 simulations (37 %). Induction was more rare for  $g_{CaL}$  values outside this range. The induced activity resembled AF in some cases and atrial flutter in others.

The model used here had no electrophysiological heterogeneity and no fibrosis. A previous study by McDowell et al. [12] found that AF induction by rapid pacing was only possible when a considerable amount of fibrosis was present. Differences in model anatomy may have contributed to this contrasting finding, but the studies also had different pacing protocols and different electrophysiological parameters. While both studies used parameters mimicking the changes found in AF patients, such as a 70 % reduction of  $g_{CaL}$  [13], the maximum conductivities of the potassium currents differed. In particular, this study used a doubled  $g_{K1}$  [14] while McDowell et al. used a value slightly below normal [12]. Consequently, the cycle length in their model was about 260 ms while it was approximately 150 ms in this study. This very short cycle length corresponds to observations in atrial myocytes from AF

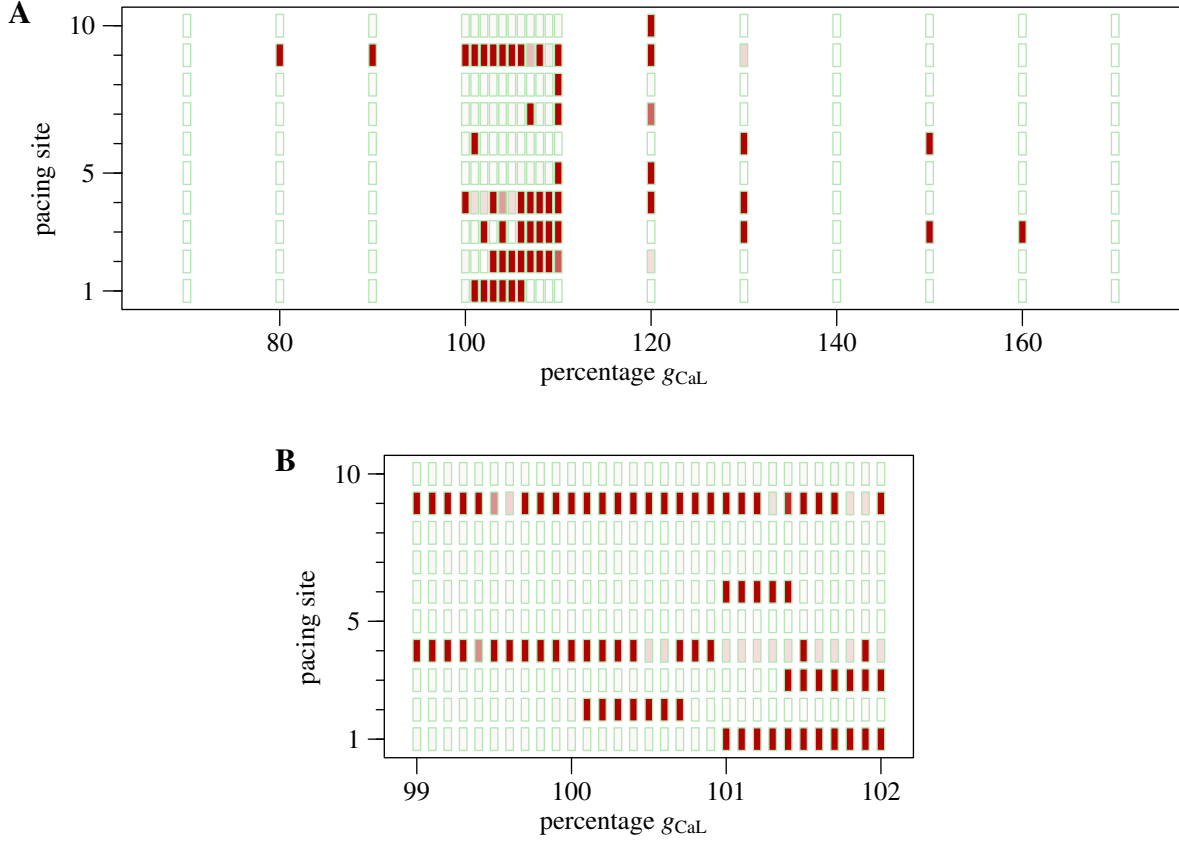


Figure 2. **A:** AF induction as a function of  $g_{CaL}$  for each of the 10 pacing sites. Each green rectangle represents a simulation. Dark red filling indicates that there was still propagating activation after 10 s, white filling indicates that the activity ended within 150 ms of the last pacing pulse, and shades of pink indicate short runs of self-sustained activity. **B:** Zoom-in on the range  $0.99 \leq g_{CaL} \leq 1.02$ , where simulations were performed at 0.1-percent increments of the parameter value. The format is the same as in panel A.

patients [14] and the corresponding dominant frequency of 6.7 Hz is within the range of measured values [15].

The electrophysiological properties of the human atria are thought to be heterogeneous and this heterogeneity can be included in models [16]. Moreover, the autonomic nervous system can amplify local heterogeneities by releasing acetylcholine, which activates an additional outward current [17]. In this study these heterogeneities were consciously omitted, because the purpose was to investigate the role of (normal) structural heterogeneities alone.

For this study the Courtemanche et al. model [9] was adapted to interpolate discontinuities in its rate coefficients. Although these discontinuities are very small, they occasionally amplify round-off errors and thus lead to non-reproducible results on multiprocessor systems where the order of some operations depends on machine conditions. Previous tests with the same anatomical model but without the adaptations in the ionic model had shown that this could lead to different results when simulations were repeated on different machines, with a different number of

processors, or even when they were repeated with all controllable parameters identical. The fact that 20 simulations yielded exactly the same results on two different supercomputers with different numbers of processors employed demonstrates that these modifications to the model equations suffice to make the simulations deterministic. Consequently, the results of this study were not affected by the use of two different computers or by non-deterministic calculations. Similar approaches to interpolate discontinuities have been used by others, for example to make the model equations differentiable [18]. An alternative method to obtain deterministic results is to impose a fixed order in the inter-process communication, but this reduces performance and would still allow different outcomes on different hardware configurations.

Another reason to remove discontinuities from ionic model equations could be the suspicion that they are involved in spiral breakup, but this has previously been ruled out by Panfilov et al. [19].

In conclusion, this study suggests that electrical remodel-

eling and an ectopic focus suffice to start AF, and thus may precede structural remodeling. However, it remains to be investigated whether this would be possible with a smaller amount of electrical remodeling.

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